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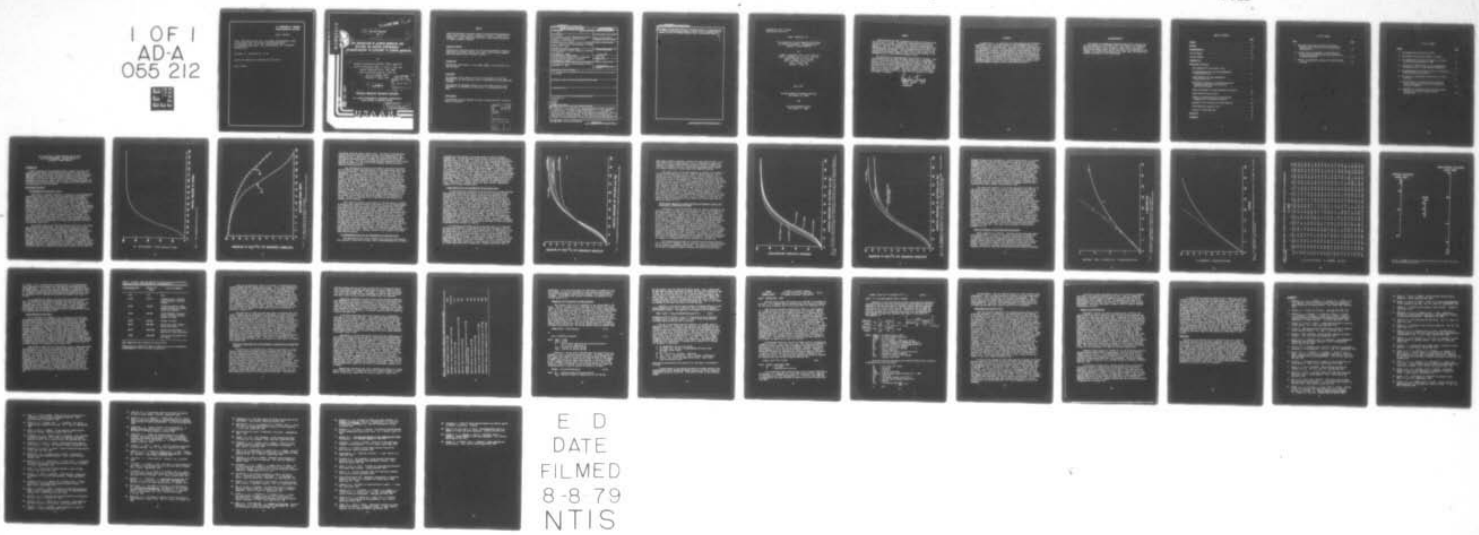

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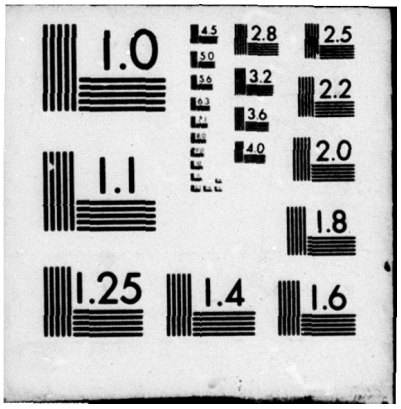
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Joseph C. Denniston, et al

Avaition Medicine Research Division

April 1978

USAARL REPORT
78-7

THE INTERACTION OF CARBON MONOXIDE AND ALTITUDE ON AVIATOR PERFORMANCE: PATHOPHYSIOLOGY OF EXPOSURE TO CARBON MONOXIDE.

By

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April 1978

Aviation Medicine Research Division

U.S. ARMY AEROMEDICAL RESEARCH LABORATORY
FORT RUCKER, ALABAMA 36362

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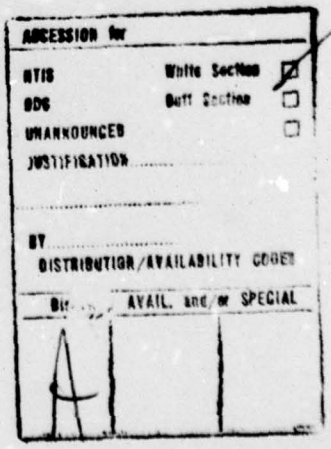

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A reappraisal of the interaction of carbon monoxide and altitude is presented in light of current concepts of the pathophysiology of low level exposure to carbon monoxide. The review includes a discussion of: (1) the potential sources of carbon monoxide; (2) the factors affecting the absorption, transport, and elimination of carbon monoxide; (3) the effects of carbon monoxide on human health and cognitive function; (4) the interaction of carbon monoxide and altitude, and resulting hypoxia; (5) the concept of equivalent physiological →

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altitudes; (6) predictable effects of transient elevation in carbon monoxide; (7) limits of carbon monoxide exposure; and (8) the basic pathophysiological changes occurring with hypobaric hypoxia and/or carbon monoxide hypoxia.

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The Interaction of Carbon Monoxide and Altitude on Aviator Performance: Pathophysiology of Exposure to Carbon Monoxide

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April 1978

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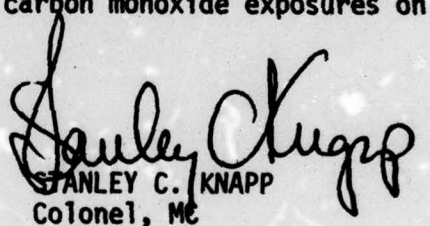
SUMMARY

Carbon monoxide has been recognized as a threat to aircrews since the early days of flight. Increasingly sophisticated aircraft and engines have provided the potential for a myriad of carbon monoxide exposures. This fact in conjunction with altitude-induced hypoxia and smoking provides the current US Army aircrewman with an insidious and life-threatening environment. The operational aviator as well as the research and development community needs a basic understanding of the pathophysiology of carbon monoxide exposure in man.

The interaction of carbon monoxide and altitude is reviewed. Data are presented which show that the modest smoker with 7% carboxyhemoglobin in his blood and flying at an actual altitude of 5,000 feet is actually flying at an equivalent physiological altitude of 10,500 feet. The performance decrement associated with this hypoxic state may represent the critical loss in operational skill required to accomplish the mission in a combat environment. Continued research into the physiologic and psychologic effects of carbon monoxide exposures on aviator performance is ongoing.



STANLEY C. KNAPP
Colonel, MC
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ABSTRACT

A reappraisal of the interaction of carbon monoxide and altitude is presented in light of current concepts of the pathophysiology of low level exposure to carbon monoxide. The review includes a discussion of: (1) the potential sources of carbon monoxide; (2) the factors affecting the absorption, transport, and elimination of carbon monoxide; (3) the effects of carbon monoxide on human health and cognitive function; (4) the interaction of carbon monoxide and altitude, and resulting hypoxia; (5) the concept of equivalent physiological altitudes; (6) predictable effects of transient elevation in carbon monoxide; (7) limits of carbon monoxide exposure; and (8) the basic pathophysiological changes occurring with hypobaric hypoxia and/or carbon monoxide hypoxia.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

THE INTERACTION OF CARBON MONOXIDE AND ALTITUDE ON AVIATOR PERFORMANCE: PATHOPHYSIOLOGY OF EXPOSURE TO CARBON MONOXIDE

INTRODUCTION

A basic knowledge of the pathophysiological changes that occur with hypobaric hypoxia and/or carbon monoxide (CO) hypoxia is essential to understanding and minimizing the resultant effects on aviator performance. Importantly, exposure to either the reduced barometric pressure (P_B) of altitude or to CO has the same end effect--a reduction in oxygen (O_2) available to the tissues. Hence, the net effect of hypobaric hypoxia and CO hypoxia on aircrew performance will in large part be determined by the resultant degree of cellular hypoxia.

REVIEW AND DISCUSSION

The Oxyhemoglobin Dissociation Curve

The effects of hypobaric hypoxia or CO hypoxia on the oxyhemoglobin dissociation (O_2Hb) curve (Fig. 1) must be understood at the onset in order to grasp clearly the resultant effects on aviator performance. Figure 1 depicts the relationship between the O_2 saturation (So_2) of hemoglobin (Hb) and the arterial oxygen tension ($P_{a}o_2$)--the higher the $P_{a}o_2$ the greater the amount of Hb bound with O_2. Thus, it becomes immediately apparent when considering Dalton's Law, the alveolar gas equation and the O_2Hb dissociation curve that the reduction in P_B that occurs during ascent in altitude results in a progressive fall in So_2; hence, there is a reduction in O_2 content (Co_2; mℓ O_2/100 mℓ blood). This is depicted in Fig. 2 for a hypothetical situation (Fig. 2(A)) in which the alveolar ventilation ($\dot{V}_A$) remains constant throughout ascent to altitude. Fortunately, the chemoreceptors sense the fall in $P_{a}o_2$ with ascent and initiate an increase in $\dot{V}_A$ (46) which results in a more favorable situation (Fig. 2(B))--the Co_2 is maintained at a higher than expected level due to the increased ventilation.

The sigmoid shape of the O_2Hb dissociation curve (Fig. 1) has important physiological significance. The upper flat portion of the curve (above a $P_{a}o_2$ of 70 mm Hg) indicates that over a considerable portion of the curve a change in $P_{a}o_2$ will not markedly affect the So_2 and, hence, Co_2. In other words, the Hb is saturated almost fully with O_2 in this range, providing a wide margin of safety. Thus, it can be appreciated that under resting conditions in a normal individual ascent to moderate altitude has no appreciable effect on Co_2. For example, it can be seen from Fig. 2(B) that ascent from sea level to 5,000 feet in a normal resting individual causes only a 2.6% decrease in O_2 content. Although this small decrement in Co_2 has no appreciable effect on the normal resting individual, it can have impact on a subject's working capacity and on certain specific

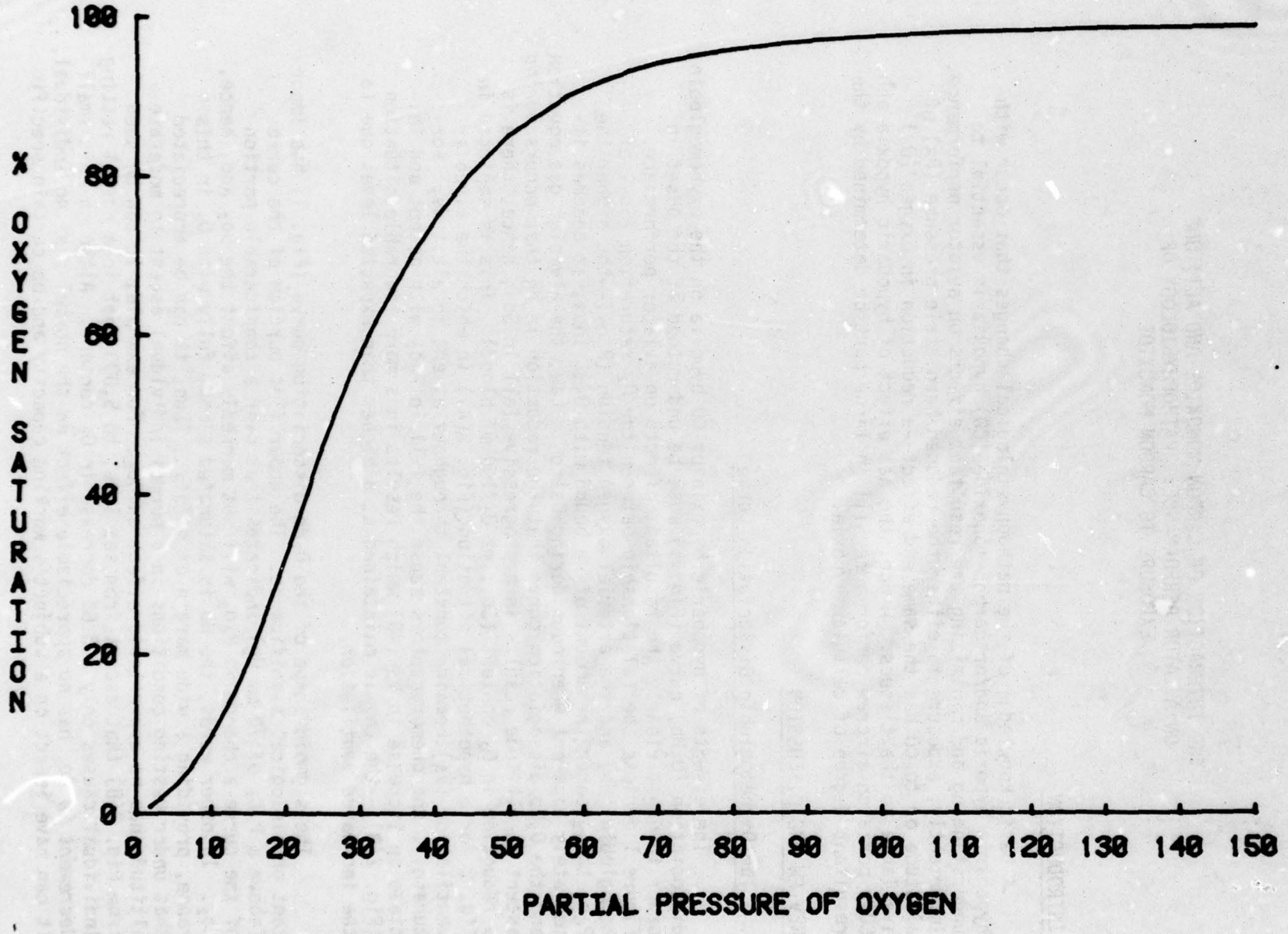

Fig. 1. The oxyhemoglobin dissociation curve.

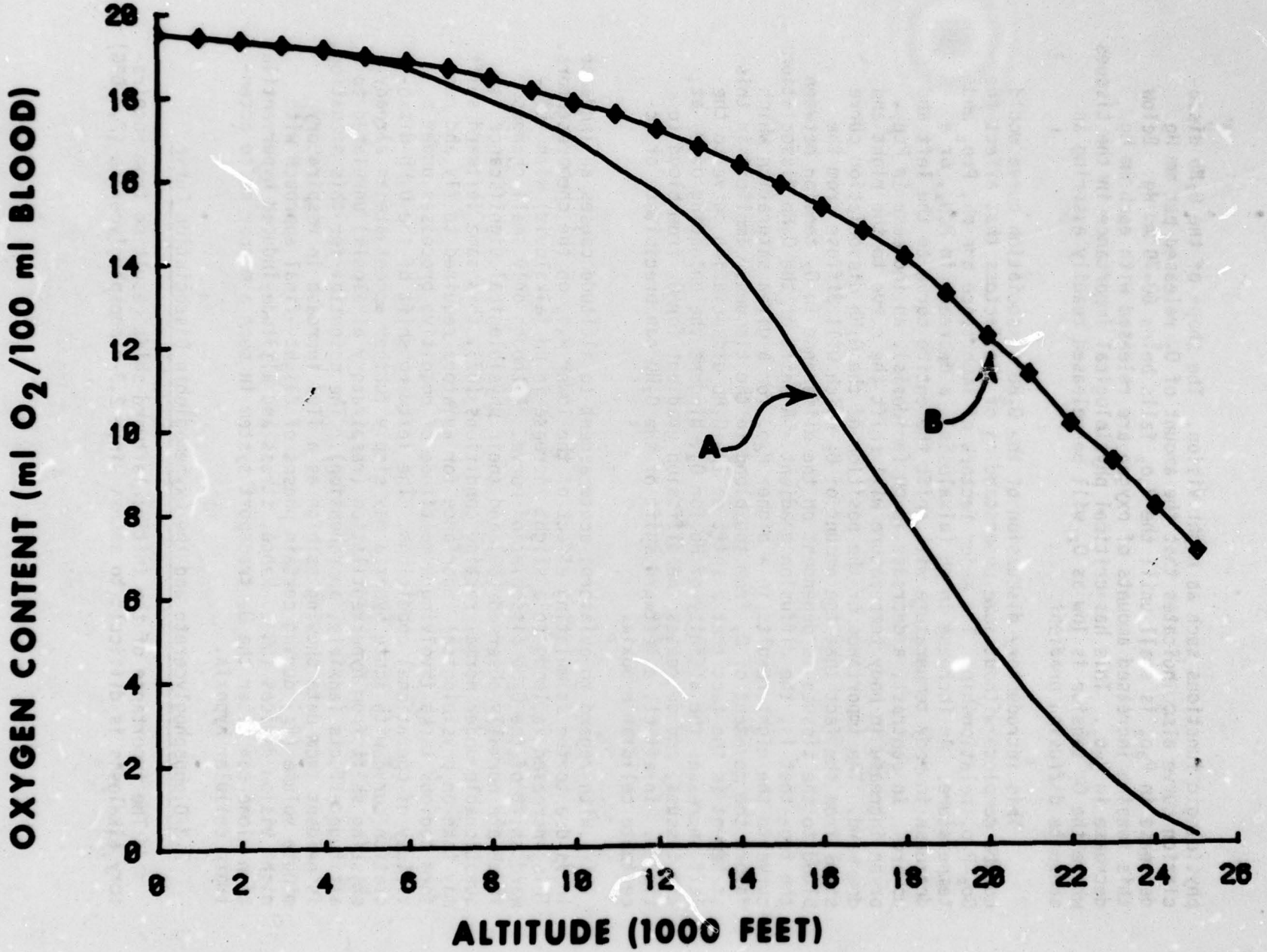

Fig. 2. The oxygen content during ascent to altitude.
A = constant alveolar ventilation. B = increasing alveolar ventilation.

physiologic functions such as night vision. The shape of the O_2Hb dissociation curve also indicates that the amount of O_2 released per mm Hg decrease in P_aO_2 is small until the P_aO_2 falls below 60-70 mm Hg. Below this tension increased amounts of oxygen are released with each mm Hg decrease in P_aO_2. This has critical physiological importance in the tissues where the O_2 tension is low as O_2 will be released readily assuring an adequate diffusion gradient.

This introductory discussion of the O_2Hb dissociation curve would not be complete without some understanding of the factors that affect the So_2-P_aO_2 relationship. The major factors of importance are pH, Pco_2 and temperature. An increase in pH (alkalosis), a decrease in Pco_2, or a decrease in body temperature will shift the entire curve to the left and upward. In contrast, a decrease in pH (acidosis), an increase in Pco_2, or an increase in body temperature will shift the curve to the right and downward. The importance of the position of the O_2Hb dissociation curve stems from the fact that the amount of O_2 which will diffuse from the blood to the tissues is dependent on the difference in O_2 tension between the two--that is, the diffusion gradient. A shift of the O_2Hb dissociation curve to the right results in a higher P_aO_2 for a given saturation which favors the movement of O_2 from the blood to the tissues. Implicit in this statement is the fact that a shift of the O_2Hb dissociation curve to the left increases the affinity of Hb for O_2, hinders the unloading of O_2 at the tissues, and decreases the diffusion gradient for O_2 from blood to tissue. In effect, a leftward shift of the O_2Hb can precipitate or accentuate cellular hypoxia.

With regard to aviators, acute ascent to altitude causes an increase in $\dot{V}_A$ due to the stimulating effect of the lower P_aO_2 on the chemoreceptors. This increased $\dot{V}_A$ leads to a slight increase in pH (alkalosis) with leftward shift of the O_2Hb dissociation curve. Although only small changes in pH are normally observed (69) and their physiological significance is questionable under normal resting conditions (67), this same leftward shift may take on physiological importance for aviators required to fly and perform tedious tasks involving a multitude of cognitive processes under a variety of operational conditions. The leftward shift of the O_2Hb dissociation curve with acute hypoxia may simply further accentuate an already existing shift from hyperventilation (respiratory alkalosis) unrelated to altitude effects (anxiety, apprehension). The potential for this situation is evident from data showing as high as a 110% increase in respiratory minute volume ($\dot{V}_E$) during certain phases of flight--final approach with night vision devices (63). Hence, stress and altitude-induced hyperventilation alone can alter the O_2 transport system in such a manner as to accentuate cellular hypoxia.

2,3-Diphosphoglycerate and the Oxyhemoglobin Dissociation Curve

The importance of the initial leftward shift resulting from respiratory alkalosis is difficult to assess since 2,3-diphosphoglycerate (2,3-DPG)

increases to within one-half its maximum value by 6 hours of hypoxic exposure (49). 2,3-DPG decreases O_2-Hb affinity, shifting the O_2Hb dissociation curve to the right. It should be clear from previous discussions that an increase in 2,3-DPG, by shifting the O_2Hb dissociation curve to the right, increases O_2 availability to the tissues. Although individuals residing at altitude have higher levels of 2,3-DPG than those at sea level (28), it is unclear as to whether intermittent exposure to hypoxia, as occurs in aviators, will sustain elevated levels of 2,3-DPG. An additional factor to be considered is the fact that acute exposure to CO causes a significant decrease in 2,3-DPG levels (82). Whether or not the levels of CO encountered from cigarette smoking or in the operational environment of the aviator will alter the expected increase in 2,3-DPG with altitude exposure remains to be determined. However, evidence has been presented (14) suggesting that CO will inhibit a 2,3-DPG induced rightward shift in the O_2Hb dissociation curve. Importantly, it appears that CO can impair certain compensatory responses to altitude-induced hypoxia.

Carbon Monoxide and the Oxyhemoglobin Dissociation Curve

In considering the interaction of CO and altitude on aviator performance, one must understand the effects of CO on the O_2 transport system. The magnitude of the cellular hypoxia resulting from exposure to CO is related not only to the total amount of Hb bound with CO instead of O_2, but also to the effect of carboxyhemoglobin (COHb) formation on the O_2Hb dissociation curve (15,23,39). When CO combines with Hb to form COHb, it causes, in essence, a "functional" anemia (hypoemic hypoxia) by decreasing the O_2 binding capacity of the blood--that is, since less Hb is available to combine with O_2, due to the competitive binding of CO and O_2 for Hb, less total O_2 is available to the tissues. This is shown in Fig. 3 which displays the O_2Hb dissociation curves of human blood containing various amounts of COHb. Standard P_aO_2 and So_2 values (74) were used to construct the normal O_2Hb dissociation curve (0% COHb). The O_2Hb curves for 2, 5, 10 and 20% COHb were calculated from this basic data (74) and theoretical considerations (70) beyond the scope of this review. It is readily apparent from Fig. 3 that as the % COHb increases, the Co_2 decreases. Therefore, increasing amounts of COHb will predispose an individual to cellular hypoxia by decreasing the available O_2 reserve.

In considering the effects of CO on the O_2Hb curve, it is important to realize that normally (in the absence of CO) only the upper portion of the O_2Hb curve (Fig. 3) is used in O_2 unloading (69). In other words, since the mixed venous Co_2 content is normally 14.3 vol % (71), a large portion of the Co_2 is present as a reserve that is only drawn upon during work or in certain disease situations. In light of this large O_2 reserve, it becomes apparent why in a normal, healthy sedate individual at sea level large amounts of COHb appear to be "well tolerated." In fact, in normal resting subjects at sea level conversion of up to one-third of the Hb to COHb does not affect appreciably the O_2 uptake (69). However, above this level of

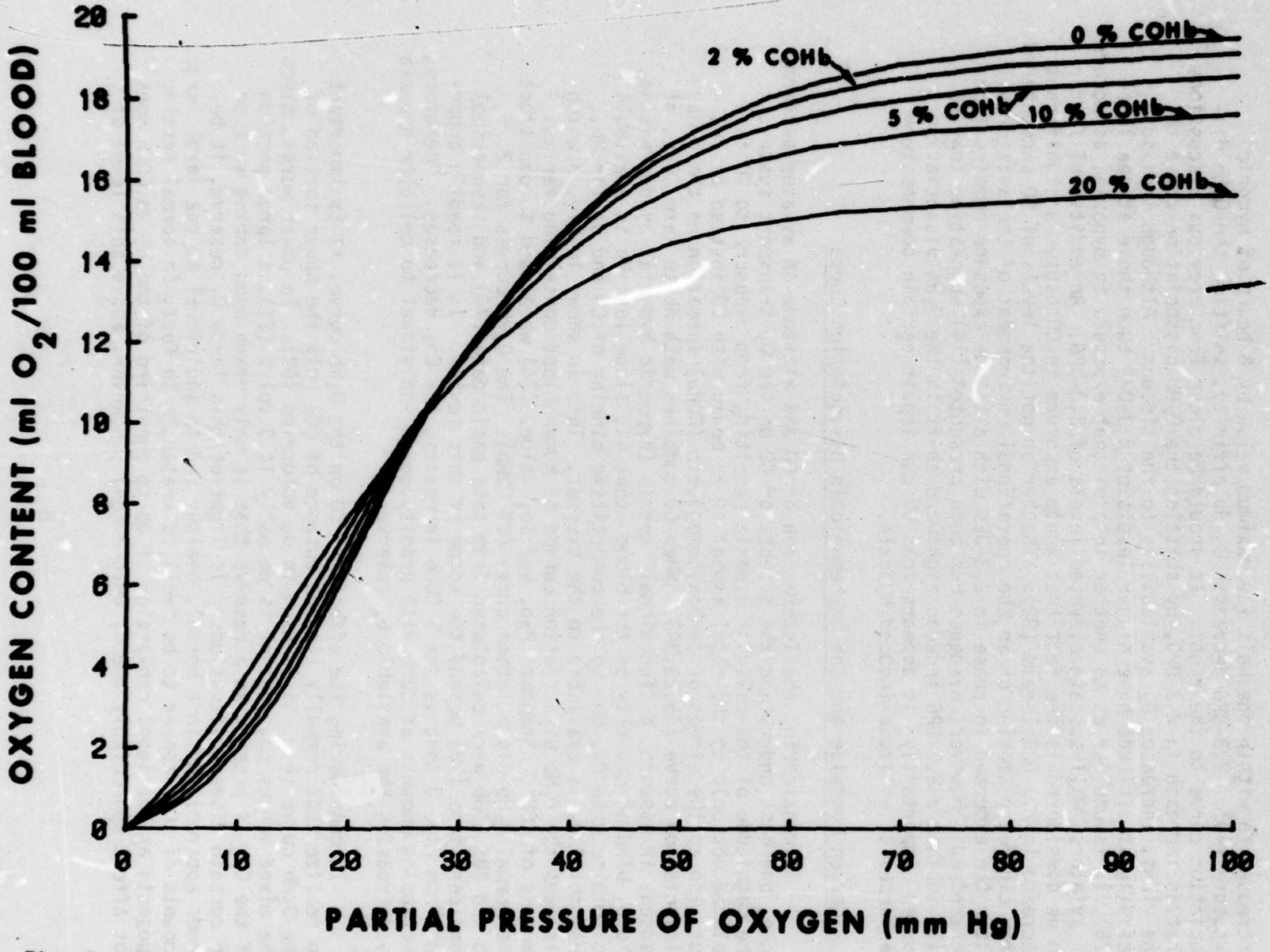

Fig. 3. The oxyhemoglobin dissociation curve as a function of various concentrations of COHb.

COHb normal subjects frequently collapse with light exercise (69). It is thus apparent that although moderate levels of COHb have no appreciable effect on O_2 reserve, the concurrent presence of hypobaric hypoxia from altitude, O_2 demands of work, or underlying disease may quickly exhaust this reserve resulting in severe hypoxia and impaired function.

The second factor in CO-induced hypoxia is related to the change in affinity of the remaining Hb for O_2. When CO combines with Hb, the remaining Hb has an increased affinity for O_2. This is depicted in Fig. 4 showing the effect of the presence of varying amounts of COHb on the O_2Hb dissociation curve of the remaining Hb. These curves were calculated from standard P_aO_2 and So_2 values (74) and theoretical considerations (70) beyond the scope of this review. It is apparent from these data that as the % COHb increases, the O_2Hb dissociation curve shifts to the left and becomes less sigmoid in character. This increase in affinity of Hb for O_2 means that O_2 is more rigidly bound to Hb. This makes the unloading of O_2 in the tissues more difficult, lowers the O_2 diffusion gradient, and sets the stage for tissue hypoxia. The mechanism of the leftward shift in the O_2Hb dissociation curve is explained by the preferential binding of CO over O_2 at the most labile O_2 sites (33). It is of interest to note that the degree of hypoxia encountered with 10% COHb is more severe than with an equivalent anemia (Fig. 5).

Physiological Responses to Carbon Monoxide and Hypobaric Hypoxia and the Concept of Equivalent Altitudes

Classically, it has been believed that P_aO_2 remains unchanged in the presence of COHb (15,50,68), and this accounts for the lack of response of the chemoreceptors (no increase in ventilation). Hence, the increase in $\dot{V}_A$ observed in hypobaric hypoxia that increases the P_aO_2 (the Co_2 is maintained at a higher than expected level, Fig. 2(B)) is not observed during CO inhalation. It is important to note that evidence has been presented which indicates that prolonged exposure (as compared to transient exposure) to CO will induce hyperpnea in response to a brain-cerebriospinal fluid acidosis (72). Recent data (7,15,16) indicate that the tissue hypoxia resulting from increasing amounts of COHb may be markedly accentuated by arterial hypoxemia in individuals with cardiopulmonary disease or in normal individuals who develop abnormal ventilation-perfusion ratios. The arterial hypoxemia that develops in these individuals is a result of the CO-induced changes in the O_2Hb curve (16). Importantly, the presence of even minor underlying cardiopulmonary disease (acute or chronic) may further accentuate the severity of hypoxia encountered by CO inhalation. Further, CO inhalation appears to accentuate the arterial hypoxemia of altitude (14).

The evidence presented thus far indicates that equivalent desaturation of Hb by CO or hypobaric hypoxia should not result in equivalent physiological changes or performance decrements. The compensatory response to the low P_aO_2 of hypobaric hypoxia increases the P_aO_2 and cardiac output

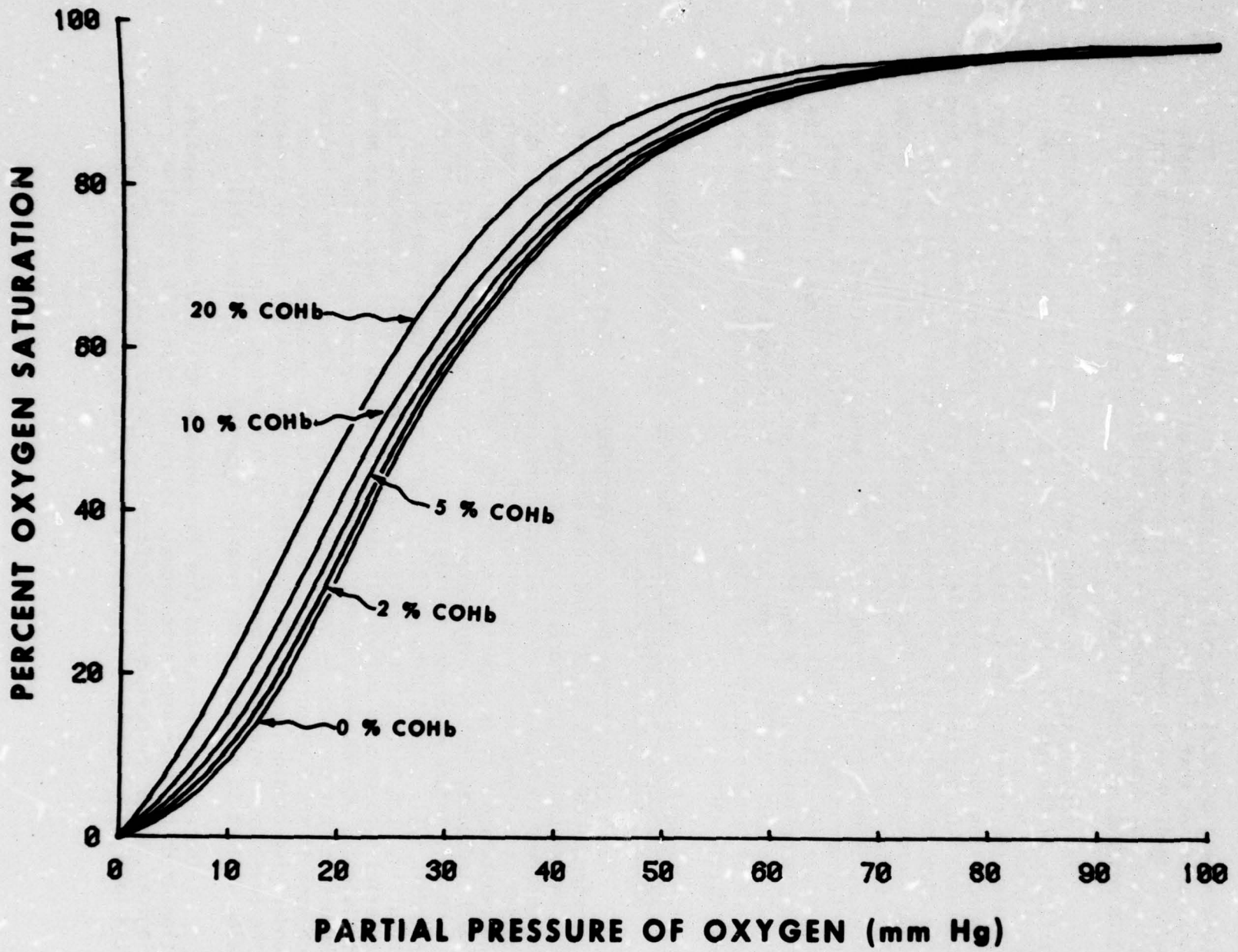

Fig. 4. The effect of COHb formation on the oxyhemoglobin dissociation curve of the remaining unbound Hb. Note that the partial pressure of oxygen at a given oxygen saturation decreases with increasing concentrations of COHb.

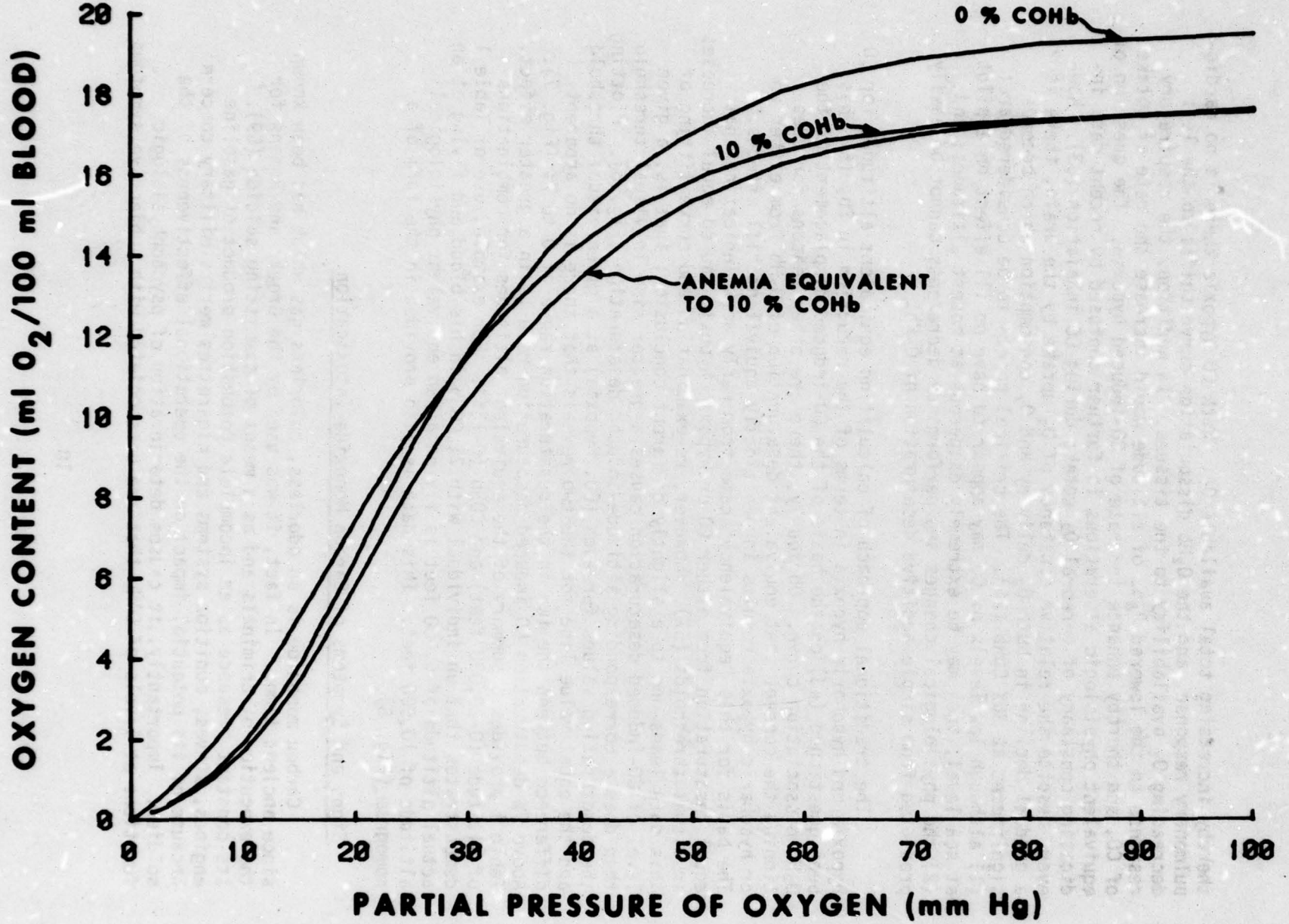

Fig. 5. The oxyhemoglobin dissociation curve as a function of COHb concentration and anemia. Note the rightwa shift in the oxyhemoglobin dissociation curve for a 10% anemia as compared to 10% COHb.

thereby increasing total available O_2. With CO hypoxia there is no cardiopulmonary response, and the O_2Hb dissociation curve shifts to the left decreasing O_2 availability to the tissues. In addition, the respiratory response to the lowered P_aO_2 of altitude would increase the rate of uptake of CO, and thereby enhance the rate of CO-induced hypoxia. The question of equivalent physiologic alterations is further confused by recent data indicating constancy of cerebral O_2 uptake during CO inhalation (83). However, despite the relative constancy of O_2 uptake by the brain, there is a gradual decline in both O_2 delivery and O_2 consumption which becomes significant at 30% COHb (26). The critical points to be considered are: (1) although low levels of CO may appear to have no ill effect on a pilot at sea level, they may be extremely dangerous at modest altitudes; and, (2) the physiological changes and performance decrements cannot be easily predicted from simple additive desaturation of O_2Hb.

The traditional approach of calculating equivalent altitudes for CO hypoxia and hypobaric hypoxia in terms of the reduction in So_2 (57) has been questioned (43) on the basis of the CO-induced displacement of the O_2Hb dissociation curve. Obviously, there are other reasons for questioning the concept that equivalent desaturation of O_2Hb from either CO or hypobaric hypoxia results in practically equivalent "ill effects." The basis for this "equivalency" came from early work indicating that equal desaturation from either CO or hypoxic hypoxia caused equal increases in visual thresholds (57). However, re-examination and curve-fitting of this data leads one to a slightly different conclusion; that is, a given level of CO-induced desaturation causes a greater rise in visual threshold than does a corresponding altitude-induced desaturation (Fig. 6). Plotting the desaturation values for each (CO, hypoxia) at a given visual threshold and the equal value line for the two reveals that there is no apparent difference between the two in the desaturation range of 0 to 7% (Fig. 7). Above 7% desaturation CO-induced desaturation results in a greater effect. Table 1 provides a summary of the equivalent altitudes for combinations of altitude (0-20,000 feet) and COHb (0-15%). For example, use of Table 1 demonstrates that an individual with 7% COHb in his blood and flying at an actual altitude of 5,000 feet is flying at an equivalent physiological altitude of 10,500 feet. This data is also provided in the form of a nomogram (Fig. 8).

Signs and Symptoms of Carbon Monoxide Intoxication

Carbon monoxide is an odorless, colorless gas which has been known since ancient times. In fact, it was used by the Greeks and Romans for the execution of criminals and as a means of committing suicide (59). Its constant presence as an incomplete combustion product of gasoline engines, stoves, munition systems and cigarettes merits military concern because of its potential impact on the operational effectiveness of the soldier. Importantly, it causes deterioration of psychophysiologic functions at levels of COHb that are unassociated with subjective symptoms

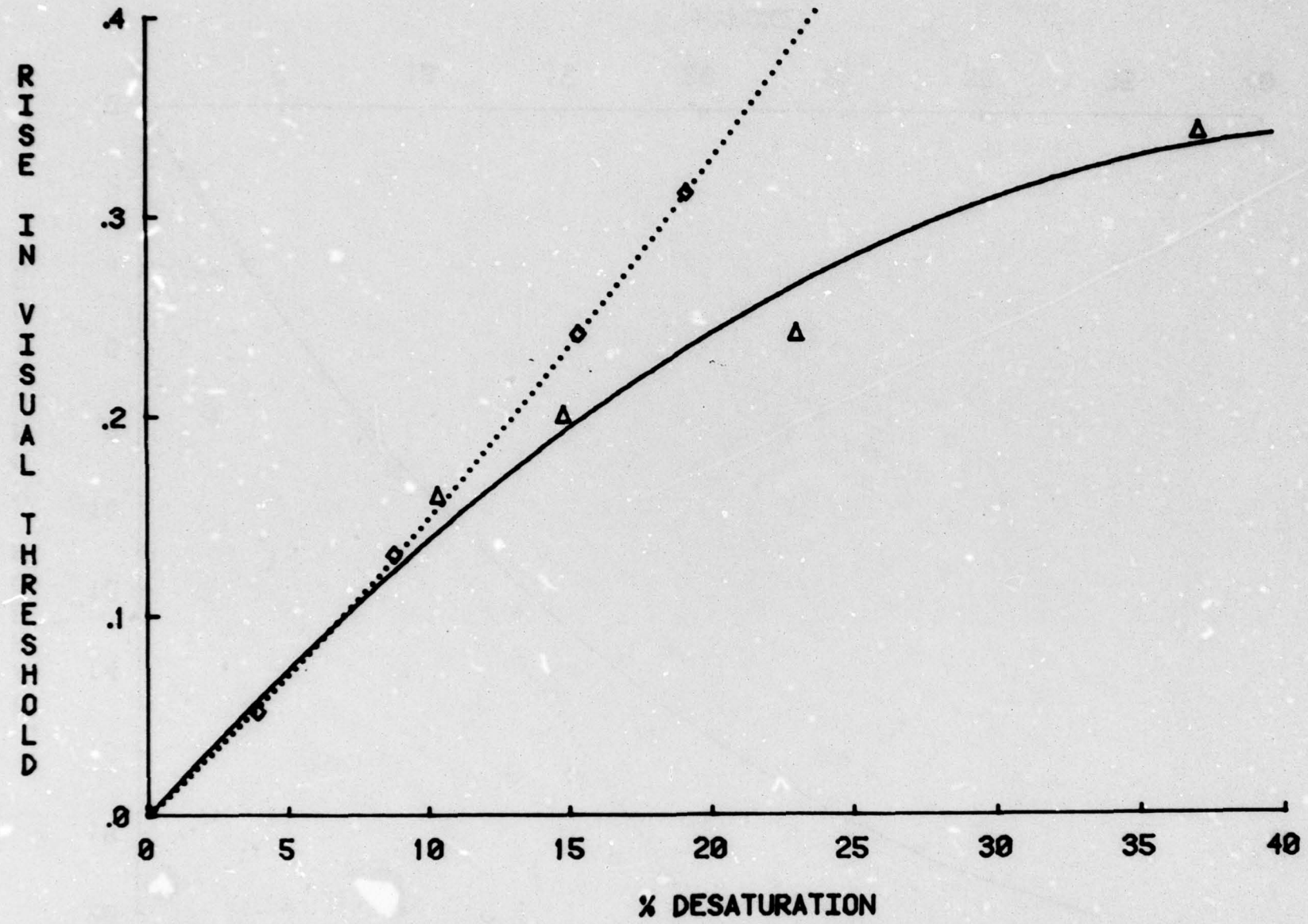

Fig. 6. The effect of oxyhemoglobin desaturation on visual threshold. Solid line = hypoxic hypoxia. Dotted line = carbon monoxide hypoxia.

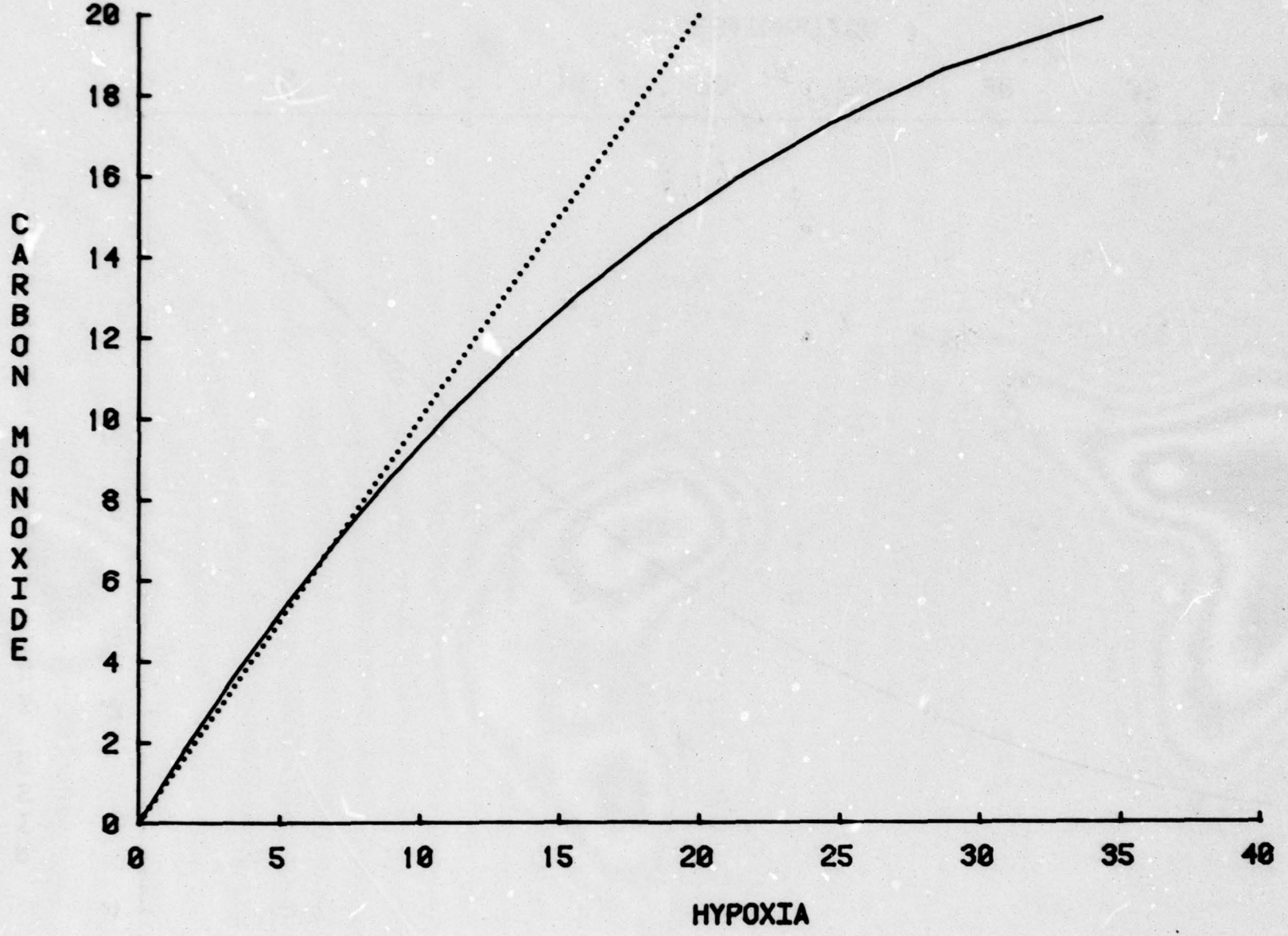

Fig. 7. The relationship of carbon monoxide and hypoxic hypoxia desaturation values for the same rise in visual threshold. Dotted line = equal value line.

Table 1. Equivalent physiologic altitude for various combinations of altitude and carboxyhemoglobin concentrations.

ALTITUDE * 1000 FEET	% COHB 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0.0	3.0	5.1	6.4	7.5	8.4	9.2	10.0	10.7	11.3	11.9	12.7	13.2	13.8	14.5
1	1.0	3.7	5.5	6.8	7.8	8.7	9.4	10.2	10.8	11.4	12.1	12.8	13.3	13.9	14.6
2	2.0	4.3	5.9	7.1	8.1	8.9	9.7	10.4	11.0	11.6	12.2	12.9	13.4	14.0	14.7
3	3.0	5.0	6.4	7.5	8.4	9.2	9.9	10.6	11.2	11.8	12.5	13.1	13.6	14.2	14.8
4	4.0	5.7	7.0	8.0	8.8	9.6	10.2	10.8	11.4	12.0	12.7	13.2	13.7	14.3	15.0
5	5.0	6.4	7.5	8.4	9.2	9.9	10.5	11.0	11.6	12.3	12.9	13.4	13.9	14.6	15.1
6	6.0	7.2	8.1	8.9	9.7	10.3	10.8	11.4	12.0	12.6	13.2	13.8	14.2	14.8	15.3
7	7.0	8.0	8.8	9.6	10.2	10.7	11.2	11.8	12.4	13.0	13.5	14.0	14.5	15.0	15.6
8	8.0	8.8	9.6	10.2	10.7	11.2	11.7	12.3	12.9	13.3	13.8	14.3	14.9	15.4	15.9
9	9.0	9.7	10.4	10.8	11.3	11.8	12.3	12.9	13.3	13.8	14.3	14.8	15.2	15.7	16.3
10	10.0	10.6	11.0	11.5	12.0	12.5	13.0	13.4	13.9	14.3	14.8	15.2	15.7	16.2	16.7
11	11.0	11.5	12.0	12.5	13.0	13.3	13.7	14.1	14.6	15.0	15.4	15.8	16.3	16.8	17.3
12	12.0	12.5	13.0	13.3	13.7	14.1	14.4	14.8	15.2	15.6	16.1	16.5	16.9	17.4	17.9
13	13.0	13.4	13.7	14.1	14.5	14.8	15.1	15.5	15.9	16.3	16.7	17.1	17.5	18.0	18.5
14	14.0	14.4	14.7	15.1	15.4	15.7	16.0	16.4	16.7	17.1	17.5	17.9	18.3	18.8	19.3
15	15.0	15.3	15.6	16.0	16.3	16.6	16.9	17.2	17.6	18.0	18.3	18.7	19.1	19.6	20.1
16	16.0	16.3	16.6	16.9	17.2	17.5	17.8	18.1	18.5	18.8	19.2	19.6	20.0	20.5	21.1
17	17.0	17.3	17.6	17.9	18.2	18.5	18.7	19.1	19.4	19.8	20.2	20.6	21.1	21.6	22.1
18	18.0	18.3	18.5	18.8	19.1	19.4	19.7	20.1	20.4	20.8	21.2	21.7	22.1	22.6	23.2
19	19.0	19.3	19.6	19.9	20.2	20.5	20.8	21.2	21.5	21.9	22.4	22.8	23.2	23.8	24.4
20	20.0	20.3	20.6	20.9	21.2	21.5	21.9	22.3	22.6	23.0	23.4	23.9	24.4	25.0	25.7

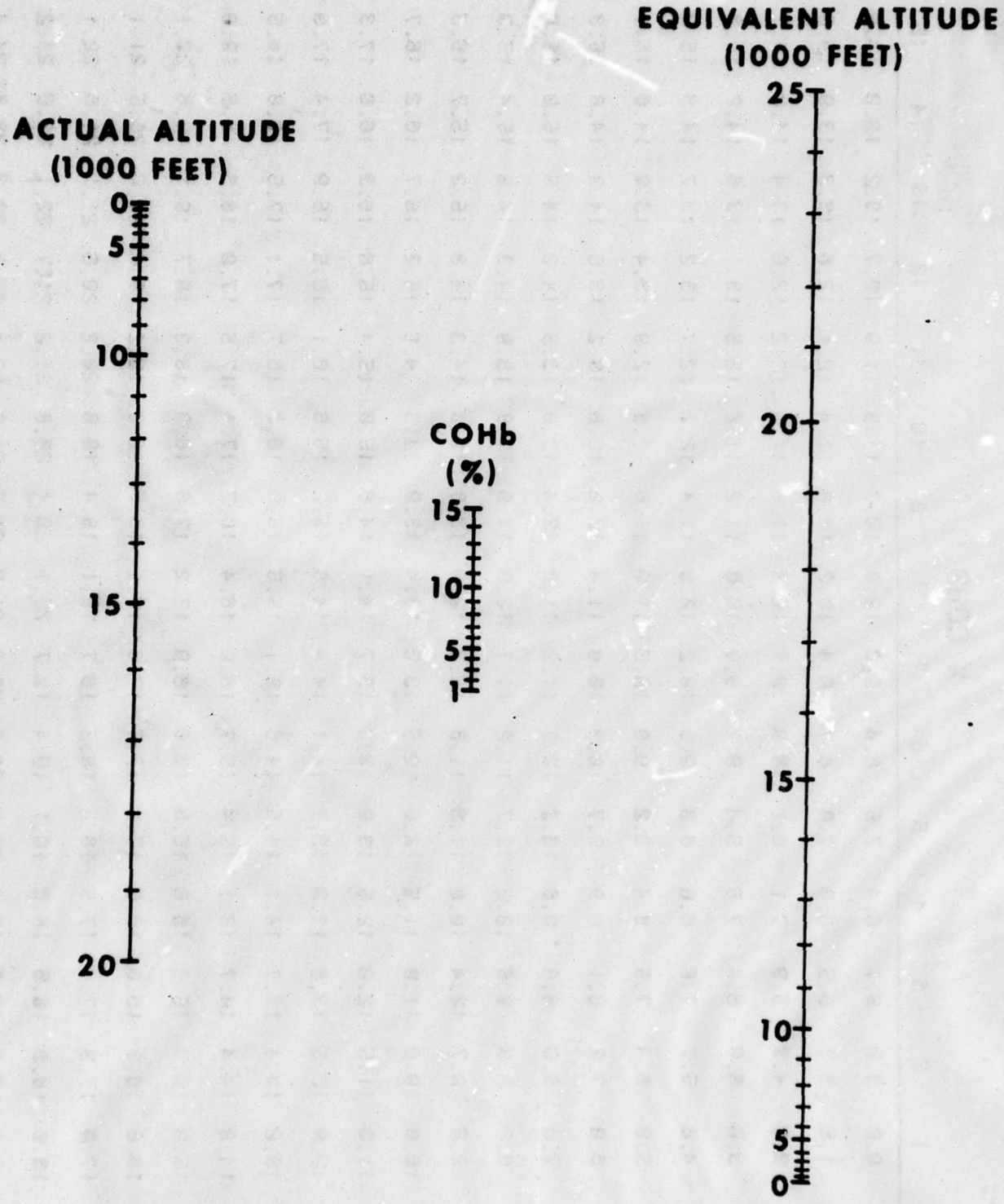

Fig. 8. A nomogram for calculating equivalent physiologic altitude from actual altitude and COHb concentration.

of illness. Thus, a mission may be jeopardized due to the psychophysiologic ineptness of an individual at a time when the individual may feel and appear normal. The clinical signs and symptoms of CO inhalation which are associated with various concentrations of COHb are summarized in Table 2. It should be emphasized that unconsciousness and death can occur without preceding signs or symptoms when exposed to extremely high levels of CO (79).

It is apparent from Table 2 that the signs and symptoms associated with 0 to 20% COHb are not different markedly from those of ordinary day-to-day ills, and, therefore, if symptoms occur the individual may not associate them with CO inhalation. For the aviator, levels of COHb considered "safe" for the ground soldier could prove extremely dangerous when combined with the effects of hypobaric hypoxia associated with flying at altitudes normally considered "safe."

Carbon Monoxide and the Heart

It is important to re-emphasize that individuals with underlying cardiopulmonary disease will be more seriously affected by CO. Evidence has been presented that clearly demonstrates that the arterial oxygen tension will be decreased significantly following CO inhalation in individuals with abnormal veno-arterial shunts or pulmonary disease (16); that is, the degree of hypoxia will be more severe in individuals with pulmonary abnormalities. Characteristically, the coronary blood flow increases with increasing % COHb as a defense mechanism to maintain myocardial oxygen requirements. The individual with coronary artery disease, however, is particularly vulnerable to myocardial hypoxia from CO, because the diseased coronary vessels may not dilate sufficiently in response to the cellular hypoxia (8). Significant myocardial changes have been observed in patients with elevation of COHb above 6% (8). Regardless of the presence of underlying cardiovascular disease, the most vulnerable target organ for low level exposure to CO appears to be the heart (33).

The potential impact of CO on the coronary system is appreciated when one contrasts the O_2 extraction of peripheral and myocardial tissues. At rest peripheral tissues normally extract about one-fourth of the O_2 available in the blood leaving a 75% reserve with an end venous Po_2 of about 40 mm Hg. In contrast, 75% of the O_2 is removed from the coronary circulation at rest leaving a 25% reserve with an end venous O_2 tension of about 20 mm Hg. During stress, peripheral O_2 requirements can be met by increased O_2 extraction and/or increased peripheral flow. However, increased myocardial requirements are primarily met by increasing coronary blood flow, since a further fall in the coronary Po_2 could precipitate serious cellular hypoxia. Thus, diseased coronary vessels that may not be able to dilate sufficiently to increase coronary blood flow lead to increased extraction at the expense of markedly reduced tissue O_2 tension (9).

Table 2. Clinical signs and symptoms of carbon monoxide poisoning associated with various concentrations of carboxyhemoglobin.*

% Carboxyhemoglobin	Ambient CO+ (ppm)	Signs and Symptoms
0-10	0-70	None.
10-20	70-160	Tightness across forehead; slight headache; exertional dyspnea.
20-30	160-280	Throbbing headache; slight nausea; abnormal fine manual dexterity; giddiness.
30-40	280-440	Severe headache; dizziness; nausea; vomiting; syncope; dimness of vision.
40-50	440-660	Syncope; collapse.
50-60	660-1000	Convulsions; coma; Cheyne-Stokes respiration.
60-70	1000-1600	Cardiac and respiratory depression; coma; convulsions.
70-80	1600-2900	Cardiac and respiratory failure; death.

*Data summarized from literature (13,32,51,73,79).

+Lowest values of ambient CO (ppm) calculated to give the corresponding carboxyhemoglobin level (see text for equations).

There are two additional factors to consider in reviewing the relationship between CO and ischemic heart disease. First, lipid accumulation in the arterial walls of cholesterol-fed animals is influenced by the air the animals breathe; that is, both hypobaric hypoxia and CO enhance the rate of lipid deposition in arterial walls (5). Interestingly, the net accumulation of lipids in the arterial walls is 3 to 5 times greater with intermittent exposure to CO than with continuous exposure (5). The second additional factor to consider is that the binding of CO to myocardial myoglobin (Mb) is 3 times greater than CO for Hb under ambient conditions (19). Under conditions of hypoxemia (P_aO_2 < 40 mm Hg), the COMb/COHb may reach 7:1. Although the O_2 transport function of Mb is impaired by CO (COMb), the significance is not entirely clear. However, it is believed that the shift of CO into the myocardium under hypoxic conditions contributes to myocardial ischemia (19).

Elevated levels of COHb also have been shown to accentuate both myocardial ischemia and the development of arrhythmias in certain individuals (8,79). COHb elevations as small as 1.6% significantly impair exercise performance in anginal patients (1,8,9); that is, an increase in venous COHb from 1.03% to 2.68% is of sufficient magnitude to cause angina pectoris to develop sooner and after less work in cardiac patients (4). Further, a COHb increase from 2.0 to 4.2% has been found to increase left ventricular and diastolic pressure by 10% and reduce myocardial performance (LV dp/dt) by 15% in ischemic heart disease patients (3). The lowered threshold for ventricular fibrillation (24,25) in the presence of COHb (< 10%) further emphasizes the relationship between sudden death and the level of CO commonly associated with smoking and/or found in the environment (2,38). Importantly, smokers have a substantially higher risk of premature coronary heart disease than nonsmokers (45). There can be no doubt that CO also acts cumulatively with other major risk factors as a contributor to coronary heart disease (64).

Effects of Carbon Monoxide on Physiological, Psychological and Cognitive Function

The effects of low concentrations of COHb on physiological, psychological, and/or cognitive function remain controversial at this time. It has been suggested that complete resolution of the conflicting reports will not be possible until research groups using double-blind studies are able to determine the precise effects of CO on the brain (79). The fact that similar studies have yielded conflicting estimates of the minimal CO level required to produce a demonstrable effect is not surprising. These conflicting reports indicate that differing experimental environments can modify behavorial patterns and/or responses just as can varying amounts of CO (11). Therefore, the details of a given study must be carefully examined in order to place experimental results in correct perspective. It is important to insure that "spare" mental capacity cannot be called into play when examining the effects of CO on mental function (86). Interestingly,

positive findings have by and large involved tests of the general population, while negative findings have been based on smaller groups of university or military personnel (86). This means, in essence, that the effects of a given level of COHb will vary depending on a host of other variables. With this in mind the key findings at low COHb levels are presented.

Measurable impairments in visual function with increasing COHb have been demonstrated by several investigators (11,36,57,65) with visual threshold increasing significantly at COHb levels as low as 4 to 5% (36,57). Visual acuity has been shown to be significantly impaired (17.5%) at 3.3% COHb (11), and decrements in peripheral vision and increases in dark adaptation thresholds are recognized at 11% COHb (56). A 26% reduction in peripheral vision has been reported in one subject smoking a pack of cigarettes a day for two weeks (44).

It has been established clearly that night vision is impaired at altitudes as low as 4,000 feet (54). The approximate percent decreases in night vision at altitudes of 5,000, 10,000, and 15,000 feet are 10%, 40% and 100%, respectively (54). In other words, nearly twice as much light is required to see a given stimulus at 15,000 feet as at sea level. These data have provided the experimental evidence for the necessity for pilots to inhale O_2 from the ground up in night flying (55). In light of these data and the concept of equivalent altitudes (Table 1), it is obvious that either smoking and/or exposure to other sources of CO will impair markedly an aviator's night vision.

Impairments of the decision making process have been demonstrated at COHb levels of between 5% and 10% (66,73). Altered choice discrimination and increases in number of errors and completion time are detectable below 5% COHb and increase with increasing COHb (73). A tenfold increase in the number of errors in choice discrimination were recognized at the 20% COHb level in the latter study. A marked and significant deterioration in the ability to detect and distinguish a specific light signal has been noted (42) at the 5% COHb level. Similarly, a significant reduction in auditory signals has been observed at less than 2% COHb (11). Recently, a marked deterioration in careful driving habits has been observed following a 3.4% increase in COHb (86). It has been noted that the loss of care, self-criticism, and impaired judgment are early manifestations of cerebral O_2 deprivation (17,86). Despite these apparent conclusive studies it has been reported that low level exposure to CO does not affect performance (60) and time perception (81) in healthy, well-motivated individuals. Table 3 provides an abbreviated summary of the effects of experimental exposure to CO on humans.

Despite the controversy that exists concerning the effects of a given level of blood COHb, it is imperative that until further evidence is forthcoming, aviators must assume that low levels of COHb will impair their

Table 3. Effects of experimental exposure to carbon monoxide on humans.

Reduction in peripheral vision at 11% COHb	(56)
Decrement in visual brightness threshold at 5% COHb	(11,36,57)
Impaired visual acuity at 3.3% COHb	(11)
Impaired depth perception and visual discrimination at 5% COHb	(65)
Impaired visual vigilance at 6.6% COHb	(42)
Decrement in discrimination of sound duration at 2-5% COHb (seriously questioned, 81,60)	(12)
Impaired auditory vigilance at 5% COHb	(29)
Impaired arithmetic performance at 5% COHb	(73)
Impairment of safe automobile driving habits at 7% COHb	(86)
Impaired ability to maintain driving distance at 10% COHb	(66)
Attentional lapses or gaps (response blocks) at 11% COHb	(56)

performance. It is this group that will additionally be exposed to hypobaric hypoxia and may well be working at near maximum capacity under a variety of environmental conditions and stresses in the operational environment. Every effort must be made to minimize the exposure of the aviation group to CO.

Absorption and Elimination of Carbon Monoxide

The ultimate effect of CO is dependent on the percent COHb in the blood. This will be determined in large part by the inspired CO concentration, the $\dot{V}_A$, duration of exposure, % COHb, and alveolar oxygen tension (47). As an individual breathes air containing CO, a state of equilibrium is reached within 6-8 hours (33) in which the CO tension (Pco) of the blood equals that of the ambient air. At this equilibrium, no net uptake or excretion of CO occurs. The fact that CO is only absorbed when the Pco in the ambient air exceeds that in the pulmonary capillaries explains why CO from smoking and CO in the air are not additive necessarily in their biologic effect (10). This can be depicted by using the Haldane equation which describes the equilibrium reached when Hb is saturated by a mixture of two gases (69). For CO the equation takes the general form:

$$(COHb)/(O_2Hb) = m(P_Ico)/(P_aO_2) \qquad [1.0]$$

or

$$P_Ico = (COHb)(P_aO_2)/m(O_2Hb) \qquad [1.1]$$

where: COHb = % COHb
O_2Hb = % O_2Hb
m = 210--a factor describing the relative affinity of Hb for CO as compared to O_2
P_Ico = inspired CO tension (mm Hg)
P_aO_2 = arterial O_2 tension (mm Hg)

Equation 1.1 can be used to determine what P_Ico would have to be exceeded in order to increase the baseline COHb. For example, what P_Ico would have to be exceeded in order to increase the basal 5% COHb level of a smoker with a P_aO_2 of 100 mm Hg and a O_2Hb of 97.5% in the absence of COHb? Substituting our knowns into equation 1.1 the P_Ico = 0.0257 mm Hg. [Remember that the O_2Hb in this case was equal to (97.5-5.0)]. Since CO is usually expressed in terms of parts per million (ppm), the following equation is used to convert CO (mm Hg) to CO (ppm):

$$CO(ppm) = (P_Ico)(10^6)/(P_B-P_{H_2O}) \qquad [2.0]$$

where: P_B = ambient barometric pressure (mm Hg)
P_{H_2O} = tension of water in inspired air at 37°C (mm Hg)

For the example given the inspired CO equals 36 ppm. Thus, a person with 5% COHb does not absorb additional CO unless the inspired CO exceeds 36 ppm. In fact, the individual would lose CO to the environment as long as the inspired CO was less than 36 ppm. This should not be interpreted to mean that a smoker is "somewhat protected" from environmental CO. Rather, his already high COHb levels will be maintained since the rate of excretion of CO from the body is also related to the ambient CO. That is, the higher the ambient CO the slower the loss of CO from the body.

Equation 1.0 can also be used to predict the percent COHb at a given ambient concentration of CO if sufficient time is allowed for complete equilibration to occur. The equation is rearranged to the following form:

$$COHb = O_2Hb/1 + [(P_aO_2)/m(COppm)(P_B-P_{H_2O})(10^6)] \qquad [3.0]$$

Assuming an O_2Hb of 97.5% at a P_aO_2 of 100 mm Hg and a P_B of 760 mm Hg, an ambient CO of 20 ppm will result in a COHb of 2.83% (from equation 3.0) when complete equilibration is achieved.

The use of the Haldane equation (equation 1.0) assumes there is negligible reduced Hb. Therefore, the equations for calculating the P_ICO (equation 1.1) at a given percent COHb and the % COHb (equation 3.0) at a given CO (ppm) only have application at near sea level conditions where the % of reduced Hb is relatively small. There are basically two ways of calculating the % COHb at equilibrium with an ambient CO at a given altitude. First, one can use equation 3.0 if an additional step is taken: determine the O_2Hb at a tension of $Po_2 + mPco$ (52). This can be demonstrated by calculating the % COHb in the blood of an individual kept at 10,000 feet until equilibrium is reached with an ambient CO of 100 ppm. The following is determined:

1. At 10,000 feet, the P_B is 523 mm Hg
2. At 10,000 feet, the P_aO_2 is approximately 58 mm Hg (from altitude vs P_aO_2 curve)
3. m = 210
4. Pco = (523-47) X (.01/100) = .048 mm Hg
5. $P_aO_2 + mPco$ = calculated Po_2 = 58 + 210(.048) = 68.08 mm Hg
6. At Po_2 = 68.1 mm Hg, the approximate % O_2Hb = 90.4% (from O_2Hb dissociation curve)

Substituting appropriately into equation 3.0, the COHb is calculated to be 13.3%.

A second method of calculating the COHb at altitude involves a different equation which combines the Haldane equation and the Hill-Barcroft equation as it applies to CO (37). This can be written in the following format:

$$\frac{[COHb]}{[COHb+O_2Hb+Hb]} = \frac{[0.00027\ (Po_2+mPco)^{2\cdot5}][mPco]}{[1+0.00027\ (Po_2+mPco)^{2\cdot5}][Po_2+mPco]} \qquad [4.0]$$

where: $COHb+O_2Hb+Hb = 100\%$

From the previous data and equation 4.0, the COHb is calculated to be 13.5%. It is apparent that no extrapolations from curves are required for the latter procedure, and it can be used under all conditions of P_B.

Thus, one can calculate a theoretical % COHb for a given ambient CO if given an infinite time for equilibration to be reached. However, the rate of CO uptake has more immediate importance in determining the effects of transient changes in CO background. Fortunately, the rate of CO uptake has been shown not to be affected by lowering the barometric pressure (increased altitude), if provisions are made to hold $P_{I}co$ constant and to correct for changes in ventilation (30,51). Interestingly, the mean level of COHb has been reported (14) to be significantly higher in smokers at 10,200 feet (6.6%) than in smokers at 1,000 feet (4.7%). The explanations offered for the higher levels of COHb were: (1) an increased CO production in the cigarettes due to a lower O_2 tension; (2) a greater rate of absorption of CO by Hb; and, (3) a slower rate of CO elimination. Increasing the barometric pressure or increasing the $P_{I}o_2$ reduces CO uptake (30,75,76) and, in fact, hastens its elimination. Generally, an average of 20% of an inhaled CO dose is eliminated within 30 minutes of exposure (31). The half-times for CO elimination have been reported to be 2.5 hours for women and 3.7 hours for men (31).

As mentioned previously, the rate of uptake of CO is influenced by a number of factors: $P_{I}co$, $P_{a}co$, $P_{I}o_2$, $P_{a}o_2$, $\dot{V}_A$, diffusing properties of capillary-alveolar membrane, rate of endogenous CO production, and the interaction of CO and O_2 with Hb (21,41,62,70). Numerous investigators have attempted to relate inspired CO and COHb (30,51,61). Studies relating the influences of concentration, duration of exposure, and degree of physical activity (30) are the accepted standard reference of the military (Air Force). A simple and less elaborate but empirical approach has recently been given by the following equation (62):

$$\%\ COHb = (CO^{0.858}t^{0.63})/197 \qquad [5.0]$$

where: % COHb = predicted % COHb
CO = CO in ppm
t = exposure time in minutes

If we assume sea level conditions and a CO of 20 ppm (2.83% COHb at equilibrium, i.e., equation 3.0), the % COHb following 30 min. exposure is calculated to be 0.57% from equation 5.0. Similarly, the % COHb can be predicted for any time following CO exposure using the following equation (62):

$$\% \text{ COHb} = [(CO^{.858}t^{0.63})/197][10^{0.00094t'}] \qquad [6.0]$$

where: t' = the post-exposure time in minutes

Equations 5.0 and 6.0 represent the best simple empirical regression equations tested for describing the absorption and elimination of CO (62). Importantly, the data were based on exposures ranging from 25 to 500 ppm of CO for up to 24 hours rather than the conventional 100 to 20,000 ppm exposures of less than 4 hours duration. The best fit for the data, however, was obtained using an equation which takes into consideration the physiological variables that determine COHb levels in the blood (21). This equation is:

$$\frac{\frac{(COHb)_t P_{O_2}}{(O_2Hb)_m} - \dot{V}co\left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}\right] - P_{Ico}}{\frac{(COHb)_i P_{O_2}}{(O_2Hb)_m} - \dot{V}co\left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}\right] - P_{Ico}} = e^{-\left[\frac{P_{O_2}t}{mVb(O_2Hb)\left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}\right]}\right]} \qquad [7.0]$$

where:
- $(COHb)_t$ = mℓ CO/mℓ blood at time t
- $(COHb)_i$ = mℓ CO/mℓ blood at time zero
- (O_2Hb) = mℓ O_2/mℓ blood
- P_{O_2} = P_{O_2} in pulmonary capillaries (mm Hg)
- $\dot{V}co$ = rate of endogenous CO production (mℓ/min)
- D_L = pulmonary diffusing capacity (mℓ/min/mm Hg)
- $\dot{V}_A$ = alveolar ventilation (mℓ/min)
- P_{Ico} = Pco of inspired air (mm Hg)
- Vb = blood volume (mℓ)
- m = affinity of blood for CO to that for O_2
- P_B = barometric pressure (mm Hg)
- P_{H_2O} = tension of water at 37°C (mm Hg)
- t = exposure time (min)

Given the following information the % COHb following 30 min. exposure to 20 ppm of CO can be calculated.

- $\dot{V}_A$ = 12.7 ℓ/min; 26.7 ℓ/min
- P_B = 760 mm Hg
- P_{H_2O} = 47 mm Hg
- O_2Hb = 0.20 mℓ O_2/mℓ blood
- $(COHb)_i$ = 0.002 mℓ CO/mℓ blood (1% COHb X 0.2 = .002)
- P_{O_2} = 100 mm Hg
- $\dot{V}co$ = .007 mℓ/min [normal value (21)]
- D_L = 30 mℓ/min·mm Hg [normal value (21)]
- Vb = 5000 mℓ
- P_{Ico} = .0143 mm Hg from $\frac{0.002}{100}$ X 713
- m = 210

The COHb equals 1.32% and 1.45% for $\dot{V}_A$ for 12.7 ℓ/min and 26.7 ℓ/min, respectively. Under the same conditions at 200 ppm of CO the % COHb would be 6.43% and 7.12%, respectively, for the two $\dot{V}_A$ in nonsmokers. Thus, it can be seen from this example that the alveolar ventilation as a physiological parameter will have a marked impact on the net COHb level at any given ambient CO. Similarly, the other parameters as outlined above will influence the net COHb levels under a specific set of conditions.

Carbon Monoxide Exposure Limits

With the foregoing knowledge of the pathophysiologic effects of CO, associated decrements in performance, and understanding of the kinetics of CO uptake and elimination, one can begin to place the effects of ambient CO, basal COHb levels, and transient exposure to high levels of CO in correct perspective. It seems clear that the emergency exposure limits (EEL; 440 ppm for 60 min.; 800 ppm for 30 min.; and 1500 ppm for 10 min.) recommended to military and space agencies by the Committee on Toxicology National Research Council (77) are unacceptably high. However, by definition, an EEL is a limit for accidental exposure which would normally not be repeated in a lifetime (53). Assuming a $\dot{V}_A$ of 70% of the ventilation cited by the Committee, the % COHb (from equation 7.0) would be approximately 21%, 27% and 20%, respectively, for the three EELs at sea level in nonsmokers. These levels of CO would not only cause clinical signs of CO poisoning, but would also result in marked impairment of cognitive and physiological function. Therefore, it is anticipated that such levels would markedly impair an aviator's ability to perform essential tasks within the operational environment. Interestingly, the continuous exposure limit of CO for 90 and 1,000 day flights in US spacecraft is 15 ppm (53,78). This limit was established on the basis that higher levels of CO might compromise the high level of judgment and performance required of pilots and other occupants of space vehicles (78). The National Research Council's Committee on Toxicology subsequently established EELs of CO, where mental acuity is required, at 1000 ppm for 10 min., 500 ppm for 30 min., and 200 ppm for 60 min. (58). The corresponding COHb levels of 11%, 17% and 14% for nonsmokers at sea level remain exceedingly high.

A review of MIL-STD-800 (20 July 1958) entitled "Procedure for Carbon Monoxide Detection and Control in Aircraft" reveals that the maximal transient CO levels allowable in military aircraft are considerably lower than the recommended EELs of the National Research Council. The exposure limits of 6000 ppm for 1 min., 1200 ppm for 5 min., 400 ppm for 15 min., 200 ppm for 30 min., and 100 ppm for 60 min. result in calculated COHb levels of 8.9%, 8.8%, 8.5%, 7.3% and 5.9%, respectively, in nonsmokers at sea level. However, it is apparent from Table 3 that these levels of COHb will impair the judgment and performance required of pilots. If the pilot were a smoker, then even further impairment of function would be anticipated. For example, a smoker with a 5% resting COHb level exposed to 400 ppm CO for 15 min. would achieve a calculated COHb level of 11.3% as compared to 8.5% in the nonsmoker.

In trying to assess the effects of CO, it is critical to recognize that there is no apparent threshold for CO (27). That is, studies on neurological function suggest a response to CO proportional to the CO concentration which extends to 0% CO. The question to be asked is how much decrement in performance and function is acceptable in the aviation environment. Obviously, the answer is none in light of today's advanced technological aircraft.

Sources of Carbon Monoxide

Geographic location, occupation, meteorological conditions and smoking habits have been found to be the principle factors affecting the COHb levels of American blood donors (80). Endogenous CO production (20) accounted for 0.45% COHb (80) which compares favorably with 0.36% COHb for normal subjects and 0.88% COHb for ward patients reported previously (21). The median range for % COHb in nonsmokers was 1.2 to 2.0% and 3.2 to 6.2% for smokers (80). Tobacco smoking was consistently associated with the highest levels of COHb. The smoking pattern and time since the last cigarette were found to be major determinants of blood COHb. Although the highest median value reported was 6.9% COHb for smokers, levels as high as 16.1% COHb for cigarette smokers (48) and 20% COHb for cigar smokers (6) have been reported. Interestingly, the % COHb has been found to be higher for smokers of filter cigarettes than for smokers of non-filtered cigarettes despite the fact that the CO yield is lower for filtered than the nonfiltered cigarettes (84). This suggests that the smoking habits of the two types of smokers is different--smokers of filter cigarettes may inhale more deeply than do smokers of nonfiltered cigarettes (50). This difference in inhalation practices is also thought to account in part for the differences in % COHb of individual smokers (22).

Cigarette smoke contains an average of 3 to 6% CO (6) and yields an average diluted concentration of approximately .04% CO (18,34) that is inspired into the lungs. If one assumes that this level of CO is maintained throughout the time course of smoking a cigarette (35), one can calculate an approximate COHb level for a nonsmoker. Using the simplest empirical equation (equation 5.0), the COHb following 5 minutes of smoking would be 2.39%.

If we assume a smoker with a resting 5% COHb level, the new COHb following 5 minutes of smoking would be approximately 6.47% based on equation 7.0 (21) and assuming a $\dot{V}_A$ of 12.7 ℓ/min. This level could be even higher depending on inhalation habits, type of cigarette and a host of other physiological variables. Of particular interest is the fact that passive smoking will also increase the COHb levels. This becomes readily apparent when one notes that levels of peak CO as high as 90 ppm were measured across the face of a subject sitting next to an individual smoking a cigarette for 10 minutes (48).

In considering the potential sources of CO it seems clear that the principal sources are cigarettes and engine exhaust. Although mean levels as high as 20 ppm have been noted in smoke filled rooms (21), it is difficult to specify expected levels. What is important is that cigarette smoke will raise the ambient CO and will probably have the greatest effect on smokers and the individuals sitting in close proximity to them. Depending on wind speed and direction, atmospheric stability, traffic density and nearby buildings, the outside ambient CO levels will range from 10 to 50 ppm (85) while higher levels will occur in poorly ventilated and congested areas. CO levels as high as 150 ppm have been recorded at an airport arrival concourse (43). An additional and extremely important source of transient CO for the aviator is associated with the firing of weapons from US Army helicopters. CO levels of 1000 ppm have been reported following firing of a 7.62 mm machine gun onboard a CH-47A (40). Assuming an alveolar ventilation of 12.7 ℓ/min and 26.7 ℓ/min (63) the COHb level achieved at 1 min. in nonsmokers would be 1.8% and 2.2%, respectively. At 5 min. the levels would be 4.9% and 6.8%, respectively. Hence, when compounded by the hypoxic effects of altitude, such levels of CO for even short periods of time can have major impact on the operational effectiveness of the aviator.

CONCLUSION

It should be realized that levels of ambient CO that are "safe" for the general population may represent "dangerous" levels for aviators. This is due to the interplay and accentuation of tissue hypoxia when CO and altitude are combined with the most of stresses acting on the aviator. The situation could be particularly life threatening in the combat environment. The dramatic effects of small decreases in O_2Hb on night vision may represent the most critical effect of low levels of CO on the aviator performing helicopter night nap-of-the-earth flight. Conditions producing 3 to 7% COHb can be expected to affect an aviator's visual acuity, night vision, depth perception and cognitive and performance requirements. Smoking and modest hypoxia from low level altitude could produce the prerequisite "equivalent" conditions. In-flight studies under operational conditions are planned to test this hypothesis.

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